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(54) Title: ROSIGLITAZONE CITRATE AND ITS USE AS ANTIDIABETIC

(57) Abstract: A citrate salt of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione and solvate thereof, preferably the hydrate, a process for preparing such a compound, a pharmaceutical composition containing such a compound and the use of such a compound in medicine.

## ROSIGLITAZONE CITRATE AND ITS USE AS ANTIDIABETIC

This invention relates to a novel pharmaceutical, to a process for the preparation of the pharmaceutical and to the use of the pharmaceutical in medicine.

5 EP-A-0 306 228 relates to certain thiazolidinedione derivatives disclosed as having hypoglycaemic and hypolipidaemic activity. The compound of Example 30 of EP-A-0 306 228 is 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (hereinafter referred to as "Compound (I)").

10 WO 94/05659 discloses certain salts of the compounds of EP-A-0 306 228. The preferred salt of WO 94/05659 is the maleic acid salt.

There remains a need for alternative salt forms which have properties suitable for pharmaceutical processing on a commercial scale.

We have now prepared and characterised a citric acid salt of Compound (I) (hereinafter also referred to as the "Citrate") specifically as the hydrate (hereinafter also referred to as the "Citrate Hydrate") that is obtained that are particularly stable and hence  
15 suitable for bulk handling and processing, especially wet milling processing.

The novel Citrate Hydrate also has useful pharmaceutical properties and in particular it is indicated to be useful for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

20 Accordingly, in a first aspect the present invention provides a citric acid salt of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione as a novel compound, preferably as a hydrate.

Citric acid is a triacid, so the citrate salts may theoretically exist in more than one stoichiometry. However at present the Citrate has been isolated only in a form which the  
25 ratio of Compound (I) to citric acid is 2:1 (molar ratio).

Accordingly, in a further aspect the present invention provides a 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione 2:1 citrate as a novel compound, preferably as a hydrate.

In the 2:1 salt the citrate anion may be associated with a proton (hydrogen atom) in addition to Compound (I) or may be associated with another cation, for example an  
30 alkali metal or ammonium cation. In this case the salt may be described as a mixed salt.

As indicated above, the preferred aspect of the present invention is a hydrate of the Citrate. Accordingly, in a further aspect the present invention provides a hydrate of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate as a  
35 novel compound.

The Citrate in which the ratio of Compound (I) to citric acid (by mole) is 2:1 has been isolated as a Citrate Hydrate in more than one form. Firstly, a Citrate Hydrate

(hereinafter also referred to as "Citrate Hydrate 1") containing variously from 5.7 – 6.2% by weight water, which is consistent with a 1:3 hydrate (3 molar equivalent of H<sub>2</sub>O = 5.6% by weight) has been isolated

Accordingly, the present invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate (molar ratio 2:1) 1:3 hydrate as a novel compound.

However, since the water content may not be fixed to exactly 3 molar equivalents, in one suitable embodiment, there is provided a Citrate Hydrate 1 characterised by:

- (i) an infrared spectrum substantially in accordance with Figure 1; and/or
- 10 (ii) a Raman spectrum substantially in accordance with Figure 2; and/or
- (iii) an X-ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 and Figure 3; and/or
- (iv) a Solid State <sup>13</sup>C NMR spectrum substantially in accordance with Figure 4.

In one favoured aspect, the Citrate Hydrate 1 provides an infrared spectrum substantially in accordance with Figure 1.

In one favoured aspect, the Citrate Hydrate 1 provides a Raman spectrum substantially in accordance with Figure 2.

In one favoured aspect, the Citrate Hydrate 1 provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3.

20 In one favoured aspect, the Citrate Hydrate 1 provides a Solid State <sup>13</sup>C NMR spectrum substantially in accordance with Figure 4.

In a preferred aspect, the invention provides a 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate, characterised in that it provides:

- 25 (i) an infrared spectrum substantially in accordance with Figure 1; and
- (ii) a Raman spectrum substantially in accordance with Figure 2; and
- (iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3; and
- (iv) a Solid State <sup>13</sup>C NMR spectrum substantially in accordance with Figure 4.

30 The Citrate in which the ratio of Compound (I) to citric acid (by mole) is 2:1 has also been isolated as a Citrate Hydrate (hereinafter also referred to as "Citrate Hydrate 2") containing approximately 0.4 - 3.8% by weight water which is consistent with a 1:0.2 to 1:2 hydrate. A particular example of Citrate Hydrate 2 contains approximately 2.6% by weight water, consistent with 1:1.4 hydrate. Additionally a further example contains

35 0.5% by weight which is consistent with a 1:0.27 hydrate.

Accordingly, the present invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate (molar ratio 2:1) containing approximately 0.4 - 3.8% water.

Alternatively the present invention provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate (molar ratio 2:1) which is a 1:0.2 - 1:2 hydrate.

The present invention also provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate (molar ratio 2:1) 1:1.4 hydrate as a novel compound.

The present invention additionally provides 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate (molar ratio 2:1) 1:0.25 hydrate as a novel compound.

However, the water content may not be fixed to exactly 1.4 or 0.27 molar equivalent. Therefore, in one suitable embodiment, there is provided a Citrate Hydrate 2 characterised by:

- (i) an infrared spectrum substantially in accordance with Figure 5; and/or
- (ii) a Raman spectrum substantially in accordance with Figure 6; and/or
- (iii) an X-ray powder diffraction (XRPD) substantially in accordance with Figure 7.

In one favoured aspect, the Citrate Hydrate 2 provides an infrared spectrum substantially in accordance with Figure 5.

In one favoured aspect, the Citrate Hydrate 2 provides a Raman spectrum substantially in accordance with Figure 6.

In one favoured aspect, the Citrate Hydrate 2 provides an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Figure 7.

In a preferred aspect, the invention provides an 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate, characterised in that it provides:

- (i) an infrared spectrum substantially in accordance with Figure 5; and
- (ii) a Raman spectrum substantially in accordance with Figure 6; and
- (iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Figure 7.

Depending on the solvent from which the Citrate is recovered, the Citrate may be obtained as a solvate other than a hydrate. Such solvates form part of the the present invention. References to the Citrate hereinafter includes solvates thereof.

The present invention encompasses the Citrate preferably as the Citrate Hydrate (including Hydrates 1 and 2) when isolated in pure form or when admixed with other materials.

Thus in one aspect there is provided the Citrate, preferably as the Citrate Hydrate, (including Hydrates 1 and 2) in isolated form.

In a further aspect there is provided the Citrate, preferably as the Citrate Hydrate, (including Hydrates 1 and 2) in substantially pure form.

5 In yet a further aspect there is provided the Citrate, preferably as the Citrate Hydrate, (including Hydrates 1 and 2) in crystalline form.

In an alternative aspect there is provided the Citrate, preferably as the Citrate Hydrate, (including Hydrates 1 and 2) in non-crystalline form.

10 Moreover, the invention also provides the Citrate preferably as the Citrate Hydrate (including Hydrates 1 and 2) in a pharmaceutically acceptable form, especially in bulk form, such form being particularly capable of being milled, especially wet-milled. The invention accordingly provides the Citrate, preferably as the Citrate Hydrate, (including Hydrates 1 and 2) thereof in a pharmaceutically acceptable form (especially in a bulk form) in a milled form, especially in a wet-milled form.

15 A suitable text describing the manufacturing processes referred to herein is "The Theory and Practice of Industrial Pharmacy" edited by Leon Lachman, Herbert A. Lieberman and Joseph L. Kanig, published by Lea & Febiger.

The invention also provides a process for preparing the Citrate, preferably the Citrate Hydrate, characterised in that 5-[4-[2-(N-methyl-N-(2-  
20 pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound (I)) or a salt thereof, preferably dispersed or dissolved in a suitable solvent, is reacted with a suitable source of citrate ion, such as citric acid or a citric acid hydrate; and optionally thereafter as required:

- (i) forming a solvate thereof;
- 25 (ii) recovering the Citrate, preferably the Citrate Hydrate;
- (iii) drying the product obtained, especially under vacuum.
- (iv) further processing the Citrate, preferably the Citrate Hydrate, in a manufacturing process, such as a milling process, especially a wet-milling process.

30 Formation of the Hydrate requires the presence of water at some stage; the water may be added as a cosolvent in the process e.g. 5 to 100 % water. However, it is also possible to provide sufficient water for hydrate formation by carrying out the reaction with exposure to atmospheric moisture, or by use of non-anhydrous solvents.

Preferably the isolated Citrate Hydrate is dried under vacuum at ambient temperature, for example 18-25°C, especially 21°C. The drying is optionally carried out  
35 over a dessicant such as phosphorus pentoxide, and optionally for an extended period for example 10-150 hours. Drying is continued until the water content becomes stable at

about 5 - 7%, for example 5.7 - 6.2%. In this way we have reproducibly isolated the hydrate form characterised above as Hydrate 1.

The isolated Citrate Hydrate may be also be dried, or Hydrate 1 further dried, under vacuum at elevated temperature, for example 50-80°C, especially 60-70 °C. The drying is optionally carried out over a dessicant such as phosphorus pentoxide, and also preferably for a period of 10-30 hours. In this way we have reproducibly isolated the hydrate form characterised above as Hydrate 2.

In general citrates may be prepared by contacting stoichiometric amounts (for example 1:1 or 1:2) of citric acid and Compound (I); alternatively an excess of the acid may be used. Mixed salts may be prepared by forming a precursor 1:1 salt *in situ* or using it pre-formed; and contacting the precursor salt with a solution containing the metal, ammonium ion, or other cation; or treating a citric acid salt such as a metal or ammonium citrate with Compound (I).

A suitable reaction solvent is a ketone, such as acetone, an ether such as tetrahydrofuran or a nitrile such as acetonitrile. Several solvents when tried did not provide product, although the before mentioned solvents were found to be suitable.

Conveniently, the source of citrate ion is citric acid or a hydrate thereof, for example citric acid monohydrate. The citric acid is preferably added as a solid or in solution or as a suspension, for example in water, ether, ketone, nitrile or a lower alcohol such as methanol, ethanol, or propan-2-ol, or a mixture of solvents. For example, solid citric acid monohydrate may be added to a solution of Compound (I) in solution, or as a suspension in, for example tetrahydrofuran.

An alternative source of citrate ion is provided by a suitably soluble base salt of citric acid, for example ammonium citrate, or the citrate salt of an amine, for example ethylamine or diethylamine.

The concentration of Compound (I) is preferably in the range 3 to 50% weight/volume, more preferably in the range 5 to 20%. The concentration of citric acid solutions are preferably in the range of 5 to 75% weight/volume.

The reaction is usually carried out at ambient temperature or at an elevated temperature, for example at the reflux temperature of the solvent, although any convenient temperature that provides the required product may be employed.

Solvates, preferably the hydrates, of the Citrate are to be prepared for example by crystallising or recrystallising from a solvent which provides or contains the solvate moiety, or by exposing the Citrate to the solvate moiety as a vapour.

Recovery of the required compound before drying comprises isolation from an appropriate solvent, optionally the reaction solvent, or alternatively a different solvent or solvent mixture. For example, the Citrate is prepared by treating Compound (I) with

citric acid or citric acid monohydrate in tetrahydrofuran, followed by evaporation or partial evaporation of the solvent, and subsequent treatment with water.

Alternatively the required compound may be isolated by crystallisation from an appropriate solvent or solvent mixture which may be initiated by use of seed crystals.

- 5 Careful control of precipitation temperature and/or the use of seeding may be used to improve the reproducibility of the product form.

Formation of a hydrate requires the presence of water at some stage. This may be added as water as the solvent, or as a co-solvent, or by exposure to atmospheric moisture.

- 10 Compound (I) is prepared according to known procedures, such as those disclosed in EP-A-0 306 228 and WO 94/05659. The disclosures of EP-A-0 306 228 and WO 94/05659 are incorporated herein by reference as if set out in full herein.

Citric acid and citric acid monohydrate are commercially available compounds.

- 15 When used herein the term 'prophylaxis of conditions associated with diabetes mellitus' includes the treatment of conditions such as insulin resistance, impaired glucose tolerance, hyperinsulinaemia and gestational diabetes. Diabetes mellitus preferably means Type II diabetes mellitus.

- Conditions associated with diabetes include hyperglycaemia and insulin resistance and obesity. Further conditions associated with diabetes include hypertension, cardiovascular disease, especially atherosclerosis, certain eating disorders, in particular  
20 the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia. Additional conditions associated with diabetes include polycystic ovarian syndrome and steroid induced insulin resistance.

- The complications of conditions associated with diabetes mellitus encompassed  
25 herein includes renal disease, especially renal disease associated with the development of Type II diabetes including diabetic nephropathy, glomerulonephritis, glomerular sclerosis, nephrotic syndrome, hypertensive nephrosclerosis and end stage renal disease.

- As mentioned above the compound of the invention has useful therapeutic properties: The present invention accordingly provides the Citrate, preferably as the  
30 Citrate Hydrate (including Hydrates 1 and 2), for use as an active therapeutic substance.

More particularly, the present invention provides the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

- 35 The Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), may be administered *per se* or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier. Suitable methods for formulating the Citrate,

preferably the Citrate Hydrate (including Hydrates 1 and 2), are generally those disclosed for Compound (I) in the above mentioned publications.

Accordingly, the present invention also provides a pharmaceutical composition comprising the Citrate preferably the Citrate Hydrate (including Hydrates 1 and 2), and a  
5 pharmaceutically acceptable carrier therefor.

The Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), is normally administered in unit dosage form.

The active compound may be administered by any suitable route but usually by the oral or parenteral routes. For such use, the compound will normally be employed in  
10 the form of a pharmaceutical composition in association with a pharmaceutical carrier, diluent and/or excipient, although the exact form of the composition will naturally depend on the mode of administration.

Compositions are prepared by admixture and are suitably adapted for oral, parenteral or topical administration, and as such may be in the form of tablets, capsules,  
15 oral liquid preparations, powders, granules, lozenges, pastilles, reconstitutable powders, injectable and infusable solutions or suspensions, suppositories and transdermal devices. Orally administrable compositions are preferred, in particular shaped oral compositions, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose,  
20 and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives  
25 such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulfate.

Solid oral compositions may be prepared by conventional methods of blending, filling, tableting or the like. Repeated blending operations may be used to distribute the  
30 active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product  
for reconstitution with water or other suitable vehicle before use. Such liquid  
35 preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example



lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

5 For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the active compound in a vehicle and filter  
10 sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that  
15 the active compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the active compound.

As is common practice, the compositions will usually be accompanied by written  
20 or printed directions for use in the medical treatment concerned.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The present invention further provides a method for the treatment and/or  
25 prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), to a human or non-human mammal in need thereof.

The compositions are formulated according to conventional methods, such as  
30 those disclosed in standard reference texts, for example the British and US Pharmacopoeias, Remington's Pharmaceutical Sciences (Mack Publishing Co.), Martindale The Complete Drug Reference (London, The Pharmaceutical Press) and Harry's Cosmeticology (Leonard Hill Books).

Conveniently, the active ingredient may be administered as a pharmaceutical  
35 composition hereinbefore defined, and this forms a particular aspect of the present invention.

In a further aspect the present invention provides the use of the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

5 In the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), may be taken in amounts so as to provide Compound (I) in suitable doses, such as those disclosed in EP-A-0 306 228, WO 94/05659 or WO 98/55122, preferably as unit doses.

10 The unit dose compositions of the invention comprise the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), in an amount providing up to 12 mg, including 1-12 mg such as 2-12 mg of Compound (I), especially 2-4 mg, 4-8 mg or 8-12 mg of Compound (I), for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 mg of Compound (I). Thus in particular there is provided a pharmaceutical composition comprising the  
15 Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), and a pharmaceutically acceptable carrier therefor, wherein the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), is present in an amount providing 1, 2, 4, 8, 12, 4 to 8 or 8 to 12 mg of Compound (I); such as 1 mg of Compound (I); such as 2 mg of Compound (I); such as 4 mg of Compound (I); such as 8mg of Compound (I); such as  
20 12 mg of Compound (I).

The invention also provides a pharmaceutical composition comprising the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), thereof in combination with one or more other anti-diabetic agents and optionally a pharmaceutically acceptable carrier therefor.

25 The invention also provides a method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), in combination with one or more other anti-diabetic agents.

30 In a further aspect the present invention provides the use of the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), thereof in combination with one or more other anti-diabetic agents, for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

35 In the above mentioned treatments the administration of the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), and the other anti-diabetic agent or agents includes co-administration or sequential administration of the active agents.

Suitably in the above mentioned compositions, including unit doses, or treatments the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), is present in an amount providing up to 12mg, including 1-12 mg, such as 2-12 mg of Compound (I), especially 2-4 mg, 4-8 mg or 8-12 mg of Compound (I), for example 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, or 12 mg of Compound (I) or 4 to 8 or 8 to 12 mg of Compound (I). Thus for example in the above mentioned compositions, including unit doses, or treatments the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), thereof is present in an amount providing 1mg of Compound (I); the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), is present in an amount providing 2 mg of Compound (I); the Citrate or a pharmaceutically acceptable solvate thereof, especially the Citrate Hydrate (including Hydrates 1 and 2), is present in an amount providing 3 mg of Compound (I); the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), is present in an amount providing 4 mg of Compound (I); or the Citrate, preferably the Citrate Hydrate (including Hydrates 1 and 2), thereof is present in an amount providing 8 mg of Compound (I).

The other antidiabetic agents are suitably selected from biguanides, sulphonylureas and alpha glucosidase inhibitors. The other antidiabetic agent is suitably a biguanide. The other antidiabetic agent is suitably a sulphonylureas. The other antidiabetic agent is suitably a alpha glucosidase inhibitor. Suitable antidiabetic agents are those disclosed in WO98/57649, WO98/57634, WO98/57635, WO98/57636, WO99/03477, WO99/03476. The contents of the above mentioned publications are incorporated herein by reference as if set out in full herein.

No adverse toxicological effects are indicated in the above mentioned treatments for the compounds of the invention.

The following Examples illustrates the invention but do not limit it in any way.

**Example 1: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 1**

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (5.0 g) was dissolved in tetrahydrofuran (50 ml) at 21°C with stirring for 20 minutes. Citric acid monohydrate (3.09 g) was added and the mixture stirred for approximately 1 hour at which point a clear solution was observed. The solvent was evaporated under reduced pressure, water (50 ml) was added and the mixture stirred vigorously for 1 hour at 21°C. The product was collected by filtration, washed with water (50 ml) and dried under vacuum over phosphorus pentoxide for 144 hours at 21°C to afford 5-[4-[2-(N-methyl-N-

(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 1 (5.3 g) as a white crystalline solid.

Water content (Karl Fisher): 6.2% wt/wt

5

<sup>1</sup>H-NMR(d<sub>6</sub>-DMSO): consistent with 5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate (2:1) hydrate.

10 **Example 2: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 1**

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (30 g) in tetrahydrofuran (300 ml) was stirred at 21°C until a clear solution was observed. Citric acid monohydrate (18.52 g) was added and the mixture stirred at 21°C until a clear solution was observed. The solvent was evaporated to give a white glassy solid. Water (300 ml) was added and the mixture stirred vigorously for 4 hours at 21°C to afford a white precipitate. The white solid was collected by filtration, washed with water (100 ml) then dried under vacuum over phosphorus pentoxide for 64 hours at 21°C to give 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 1 (33.4 g) as a white crystalline solid.

20

Water content (Karl Fisher): 5.7% wt/wt

<sup>1</sup>H-NMR(d<sub>6</sub>-DMSO): consistent with 5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate (molar ratio 2:1) hydrate.

25

**Example 3: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 1**

5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (20 g) in tetrahydrofuran (200 ml) was stirred at 21°C until a clear solution was observed. Citric acid (10.8 g) was added and the mixture stirred at 21°C until a clear solution was observed. The solvent was evaporated to give a white glassy solid. Water (200 ml) was added and the mixture stirred vigorously for 25 hours at 21°C to afford a white precipitate. The white solid was collected by filtration, washed with water (100 ml) then dried under vacuum over phosphorus pentoxide for 42 hours 40 minutes at 21°C to give 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 1 (22.2 g) as a white crystalline solid.

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<sup>1</sup>H-NMR(d6-DMSO): consistent with 5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate (molar ratio 2:1) hydrate.

5 **Characterising data recorded for the product of Example 2:**

The infrared absorption spectrum of a mineral oil dispersion of the product was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm<sup>-1</sup> resolution (Figure 1). Data were digitised at 1 cm<sup>-1</sup> intervals. Bands were observed at: 3334, 3132, 2922, 2853, 1742,  
10 1702, 1641, 1612, 1542, 1513, 1465, 1377, 1326, 1296, 1251, 1172, 1158, 1135, 1055, 1029, 1009, 931, 909, 821, 768, 739, 718, 660, 619, 604, 563, 539, 524, 510 cm<sup>-1</sup>.

The infrared spectrum of the solid product was recorded using Perkin-Elmer Spectrum One FT-IR spectrometer fitted with a universal ATR accessory. Bands were  
15 observed at: 3134, 2922, 1743, 1699, 1641, 1610, 1542, 1512, 1467, 1440, 1419, 1386, 1357, 1326, 1297, 1246, 1172, 1158, 1111, 1052, 1030, 1009, 930, 906, 821, 767, 739, 716, 659 cm<sup>-1</sup>.

The Raman spectrum of the product (Figure 2) was recorded with the sample in  
20 an NMR tube using a Nicolet 960 E.S.P. FT-Raman spectrometer, at 4 cm<sup>-1</sup> resolution with excitation from a Nd:V04 laser (1064 nm) with a power output of 400mW. Bands were observed at: 3092, 3041, 3013, 2955, 2922, 1742, 1612, 1584, 1545, 1466, 1441, 1390, 1327, 1286, 1252, 1205, 1178, 1149, 1032, 987, 918, 844, 822, 741, 719, 665, 637, 605, 495, 470, 439, 410, 336, 302, 242, 168, 114 cm<sup>-1</sup>.

25

The X-Ray Powder Diffraction (XRPD) pattern of the product (Figure 3) was recorded using the following acquisition conditions: Tube anode: Cu, Generator tension: 40 kV, Generator current: 40 mA, Start angle: 2.0 °2θ, End angle: 35.0 °2θ, Step size: 0.02 °2θ, Time per step: 2.5 seconds. Characteristic XRPD angles and relative  
30 intensities are recorded in Table 1.

Table 1

Angle	Rel. Intensity
2-Theta °	%
4.0	2.1
8.0	3
8.6	9.1

9.5	3.5
10.3	5.9
11.1	10
12.0	3.1
12.4	6.4
13.6	3.8
13.8	5.2
14.3	8.5
14.6	4.7
15.3	100
15.9	27.2
17.3	8.8
17.9	33.9
17.9	33.9
18.7	6.8
19.2	21.7
20.0	10.5
21.0	50
21.6	38.9
22.3	21
23.0	27.6
23.5	15.9
23.9	19.6
24.6	36.5
25.1	41.9
25.4	32.9
26.2	15.1
26.6	15.8
27.9	28.3
28.5	21.2
29.0	12.6
29.6	11.3
30.5	22.2
31.3	16.9
32.0	11.6
32.7	12.8
33.5	21.1
34.4	14.5

The solid-state NMR spectrum of the product (Figure 4) was recorded on a Bruker AMX360 instrument operating at 90.55 MHz. The solid was packed into a 4 mm zirconia MAS rotor

fitted with a Kel-F cap and rotor spun at ca.10 kHz. The  $^{13}\text{C}$  MAS spectrum was acquired by cross-polarisation from Hartmann-Hahn matched protons (CP contact time 3ms, repetition time 15 s) and protons were decoupled during acquisition using a two-pulse phase modulated (TPPM) composite sequence. Chemical shifts were externally referenced to the carboxylate  
5 signal of glycine at 176.4 ppm relative to TMS and were observed at: 38.3, 38.7, 39.7, 42.7, 47.7, 50.5, 55.3, 55.8, 65.8, 67.1, 74.0, 112.0, 112.6, 113.6, 114.0, 114.2, 114.6, 116.5, 128.6, 129.2, 130.3, 131.6, 132.8, 135.2, 138.7, 143.8, 144.9, 152.6, 158.1, 158.5, 171.1, 171.6, 176.5, 177.5, 178.0, 180.6 ppm.

10

### **Properties of the Citrate Hydrate 1, recorded for the product of Example 2**

#### **Solid State Stability of the Citrate Hydrate 1**

The solid state stability of the drug substance was determined by storing approximately  
15 1.0 g of the material in a glass bottle at a) 40°C / 75% Relative Humidity (RH), open exposure, for 1 month and b) at 50°C, closed, for 1 month. The material was assayed by HPLC for final content and degradation products in both cases.

a) 40°C / 75% RH: No significant degradation observed (HPLC assay 101% initial).

20 b) 50°C: No significant degradation observed (HPLC assay 98% initial).

#### **Solubility of the Citrate Hydrate 1**

The solubility of the material was determined by adding water in aliquots from 1 to 1000 ml to approximately 100 mg of drug substance until the powder had dissolved. The visual  
25 solubility was confirmed by an HPLC assay of a saturated solution.  
Solubility: 1.1 mg/ml.

#### **Example 4: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 2**

30 5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 1, product of example 1 (0.38 g) was dried under vacuum over phosphorus pentoxide at 64°C for 26 hours to give 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 2 as a white, non-crystalline solid.

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Water content (Karl Fisher): 2.6% wt/wt

**Example 5: 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 2**

5 5-[4-[2-(N-Methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 1, product of Example 1 (0.6 g) was dried under vacuum over phosphorus pentoxide at 68°C for 24 hours to give 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione citrate hydrate 2 as a white solid.

Water content (Karl Fisher): 0.5% wt/wt

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**Characterising data for the product of Example 4:**

The infrared absorption spectrum of a mineral oil dispersion of the product was obtained using a Nicolet 710 FT-IR spectrometer at 2 cm<sup>-1</sup> resolution (**Figure 5**). Data  
15 were digitised at 1 cm<sup>-1</sup> intervals. Bands were observed at: 2925, 1747, 1694, 1643, 1609, 1510, 1462, 1377, 1303, 1245, 1161, 1032, 999, 932, 832, 766, 721, 663, 603, 525 cm<sup>-1</sup>.

The infrared spectrum of the solid product was recorded using Perkin-Elmer Spectrum One FT-IR spectrometer fitted with a universal ATR accessory. Bands were  
20 observed at: 2927, 2765, 1747, 1690, 1643, 1609, 1510, 1415, 1385, 1303, 1241, 1158, 1032, 997, 930, 898, 830, 763, 737, 714, 660 cm<sup>-1</sup>.

The Raman spectrum of the product (**Figure 6**) was recorded with the sample in an NMR tube using a Nicolet 960 E.S.P. FT-Raman spectrometer, at 4 cm<sup>-1</sup> resolution  
25 with excitation from a Nd:V04 laser (1064 nm) with a power output of 400mW. Bands were observed at: 3102, 3067, 2931, 1747, 1611, 1548, 1411, 1389, 1329, 1264, 1209, 1180, 1100, 1055, 983, 921, 896, 825, 742, 666, 638, 605, 473, 399, 310, 94 cm<sup>-1</sup>.

The X-Ray Powder Diffraction (XRPD) pattern of the product (**Figure 7**) was  
30 recorded using the following acquisition conditions: Tube anode: Cu, Generator tension: 40 kV, Generator current: 40 mA, Start angle: 2.0 °2θ, End angle: 35.0 °2θ, Step size: 0.02 °2θ, Time per step: 2.5 seconds.



## CLAIMS

1. A salt of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione and citric acid, or a solvate thereof.
2. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate, or a solvate thereof.
3. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate 1:3 hydrate.
4. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate containing from 5-7 wt% water.
5. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate 1, characterised by:
- (i) an infrared spectrum substantially in accordance with Figure 1; and/or
- (ii) a Raman spectrum substantially in accordance with Figure 2; and/or
- (iii) an X-ray powder diffraction (XRPD) pattern substantially in accordance with Table 1 and Figure 3; and/or
- (iv) a Solid State  $^{13}\text{C}$  NMR spectrum substantially in accordance with Figure 4.
6. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate 1, characterised by an infrared spectrum substantially in accordance with Figure 1.
7. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate 1, characterised by a Raman spectrum substantially in accordance with Figure 2.
8. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate 1, characterised by an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3.

9. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate 1, characterised by a Solid State  $^{13}\text{C}$  NMR spectrum substantially in accordance with Figure 4.
- 5 10. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate 1, characterised by:
- (i) an infrared spectrum substantially in accordance with Figure 1; and
  - (ii) a Raman spectrum substantially in accordance with Figure 2; and
  - 10 (iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Table 1 or Figure 3; and
  - (iv) a Solid State  $^{13}\text{C}$  NMR spectrum substantially in accordance with Figure 4.
11. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate containing approximately 0.4-3.8% water.
- 15 12. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate 1:1.4 hydrate.
- 20 13. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate 1:0.27 hydrate.
14. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate 2, characterised by
- (i) an infrared spectrum substantially in accordance with Figure 5; and/or
  - (ii) a Raman spectrum substantially in accordance with Figure 6; and/or
  - (iii) an X-ray powder diffraction (XRPD) pattern substantially in accordance with
  - 30 Figure 7.
15. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate 2, characterised by:
- 35 an infrared spectrum substantially in accordance with Figure 5.

16. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate 2, characterised by a Raman spectrum substantially in accordance with Figure 6.
- 5 17. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate 2, characterised by an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Figure 7.
- 10 18. A salt according to claim 1, being 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (2:1) citrate hydrate 2, characterised by:
- (i) an infrared spectrum substantially in accordance with Figure 5; and
- (ii) a Raman spectrum substantially in accordance with Figure 6; and
- 15 (iii) an X-Ray powder diffraction pattern (XRPD) substantially in accordance with Figure 7.
19. A compound according to any one of claims 1 to 18 in isolated form.
- 20 20. A compound according to any one of claims 1 to 18 in substantially pure form.
21. A compound according to any one of claims 1 to 18 in crystalline form.
22. A compound according to any one of claims 1 to 18 in non-crystalline form.
- 25 23. A compound according to any one of claims 1 to 18 in a wet- milled form.
- 24 A compound according to any one of claims 1 to 22 in bulk form
- 30 25. A process for preparing a compound according to any one of claims 1 to 18, or a solvate thereof, characterised in that 5-[4-[2-(N-methyl-N-(2-pyridyl)amino)ethoxy]benzyl]thiazolidine-2,4-dione (Compound (I)) or a salt thereof, is reacted with a suitable source of citrate ion, optionally in the presence of water; and optionally thereafter as required:
- 35 (i) forming a solvate thereof;
- (ii) recovering the Citrate preferably the Citrate Hydrate;
- (iii) drying the product obtained.

(iv) further processing the Citrate, preferably the Citrate Hydrate, in a manufacturing process, such as a milling process, especially wet-milling.

26. A pharmaceutical composition comprising a compound according to any one of claims 1 to 24, and a pharmaceutically acceptable carrier therefor.

27. A pharmaceutical composition comprising a compound according to any one of claims 1 to 24, in combination with one or more other anti-diabetic agents and optionally a pharmaceutically acceptable carrier therefor.

28. A pharmaceutical composition according to claim 26 or claim 27, wherein the compound is present in an amount providing 1, 2, 4, 8, 12, 4 to 8 or 8 to 12 mg of 5-[4-[2-(N-methyl-N-(2-pyridyl)amino) ethoxy]benzyl]thiazolidine-2,4-dione (Compound (I)).

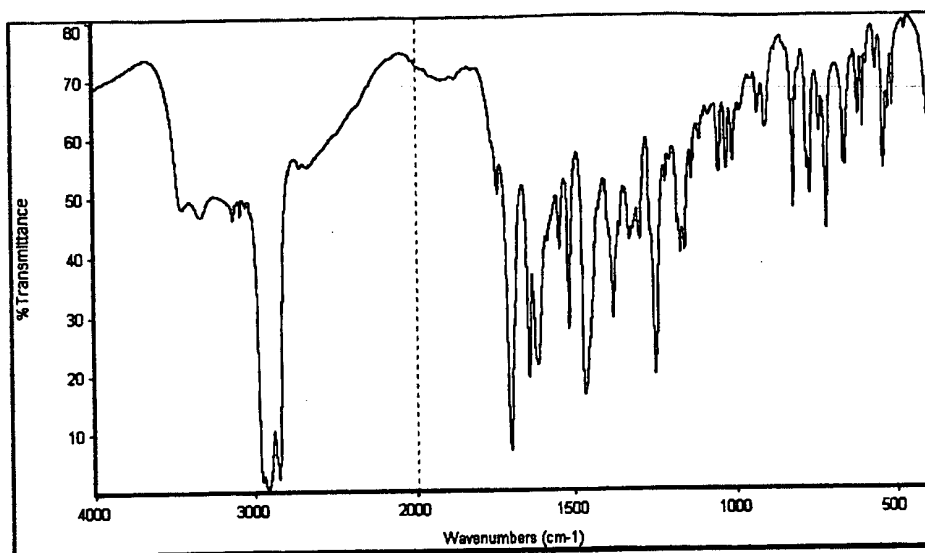
29. A compound according to any one of claims 1 to 24, for use as an active therapeutic substance.

30. A compound according to any one of claims 1 to 24, for use in the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

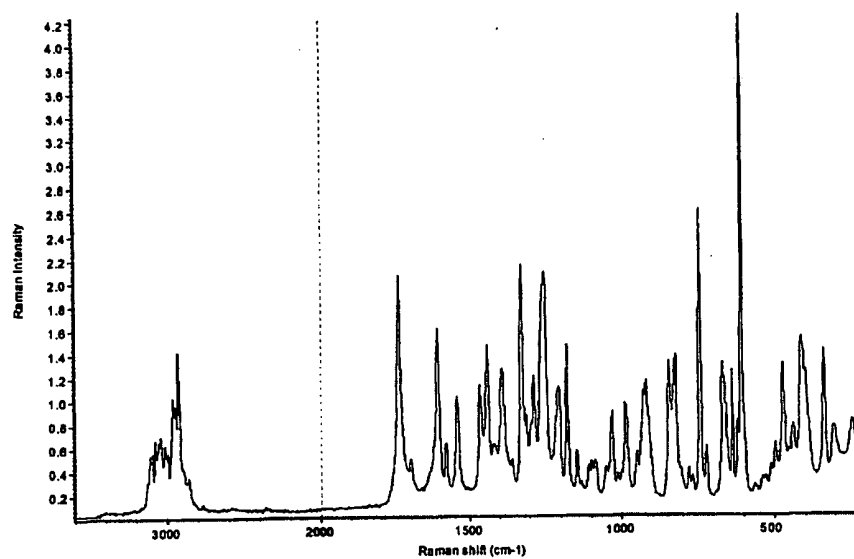
31. A use of a compound according to any one of claims 1 to 24, for the manufacture of a medicament for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

32. A method for the treatment and/or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof, in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound according to any one of claims 1 to 24, to a human or non-human mammal in need thereof.

**Figure 1** Infrared spectrum of the Citrate Hydrate 1



**Figure 2** Raman spectrum of the Citrate Hydrate 1



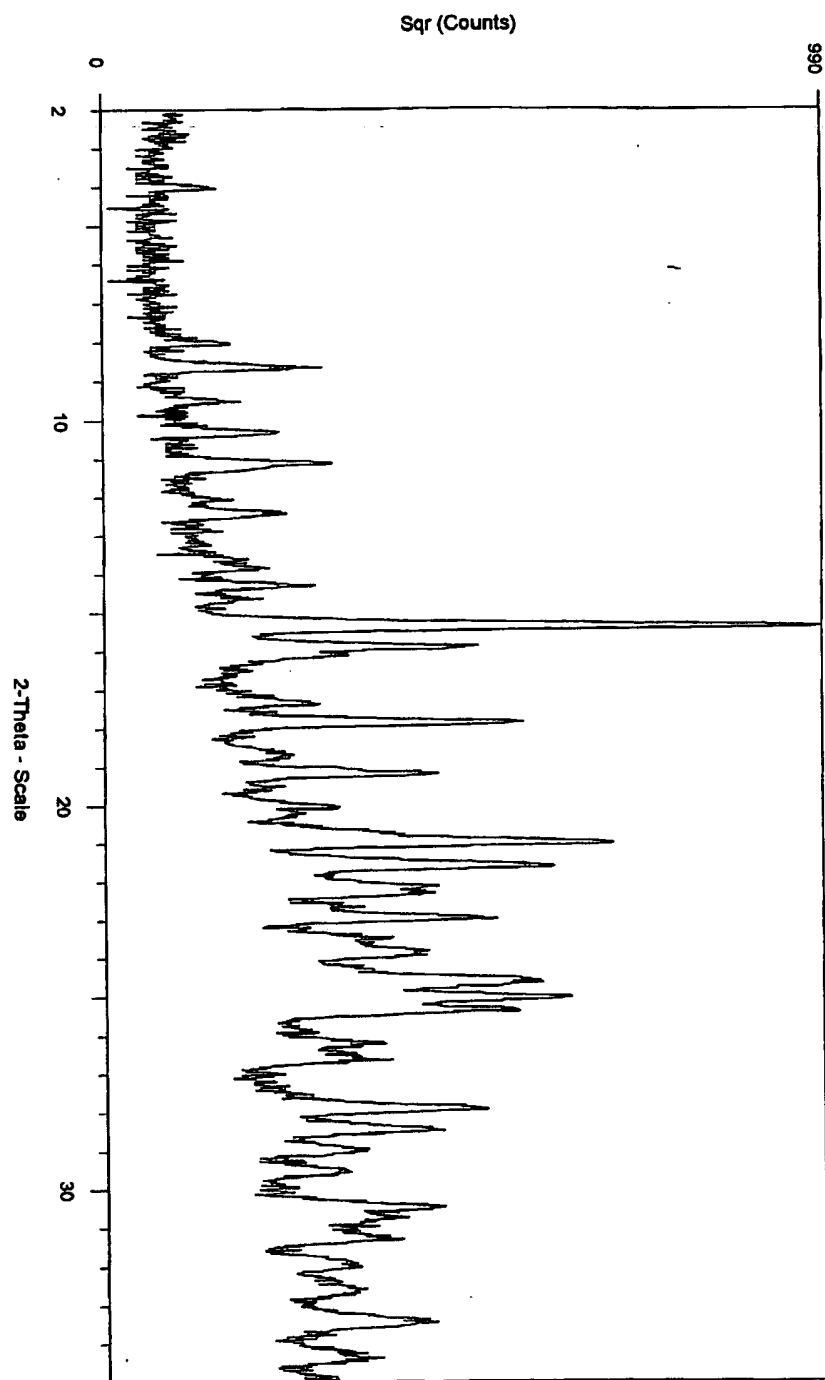
**Figure 3** X-Ray Powder Diffractogram of the Citrate Hydrate 1

Figure 4 Solid State  $^{13}\text{C}$  NMR spectrum of the Citrate Hydrate 1

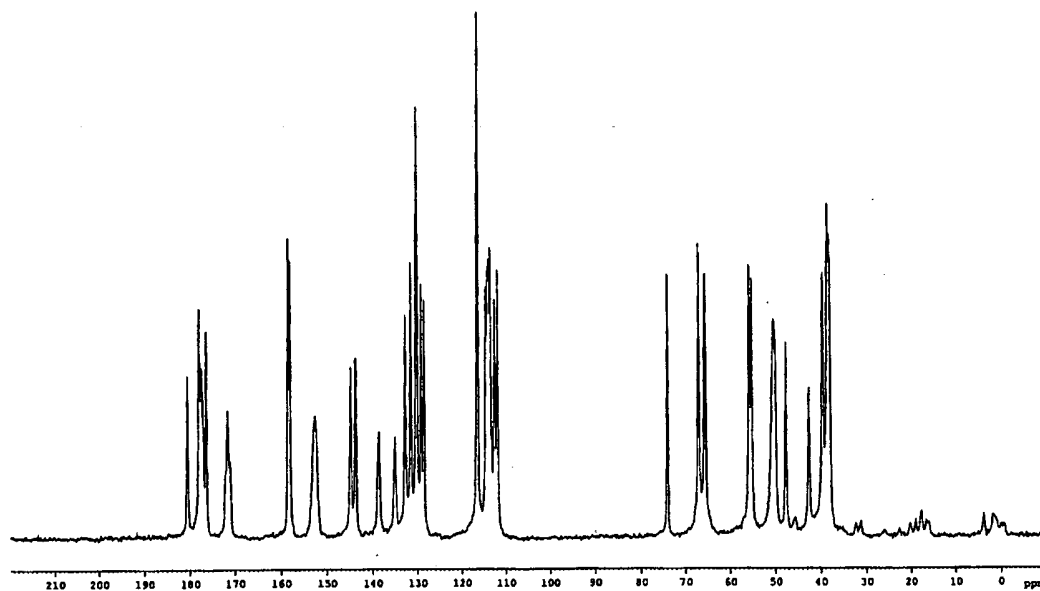




Figure 5 Infrared spectrum of the Citrate Hydrate 2

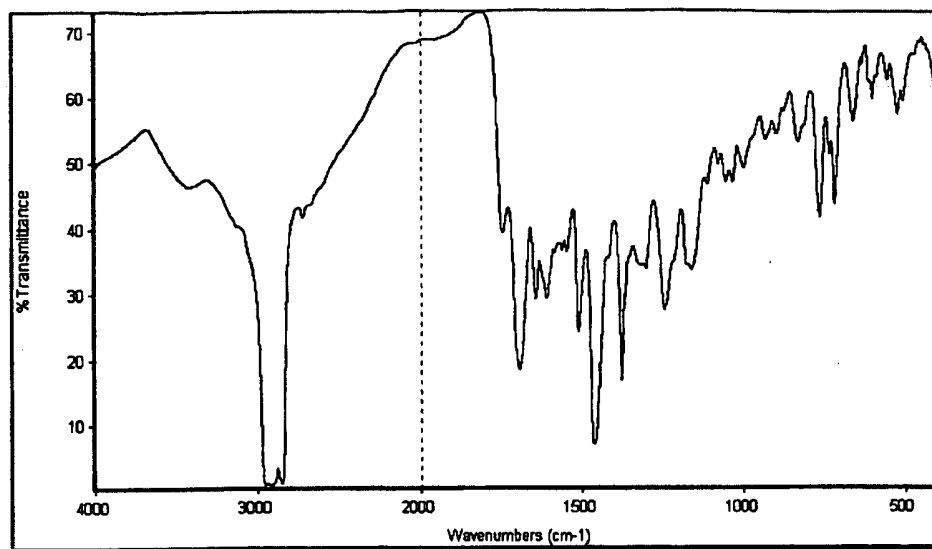


Figure 6 Raman spectrum of the Citrate Hydrate 2

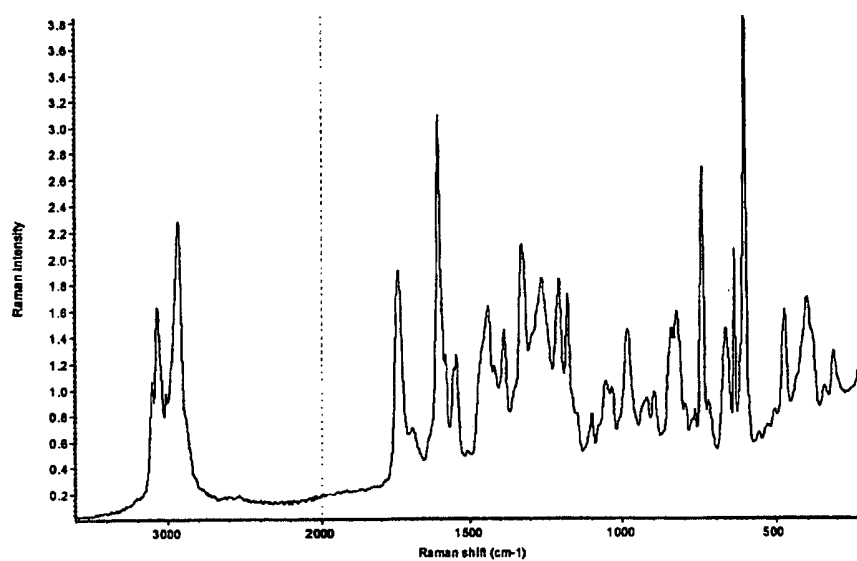
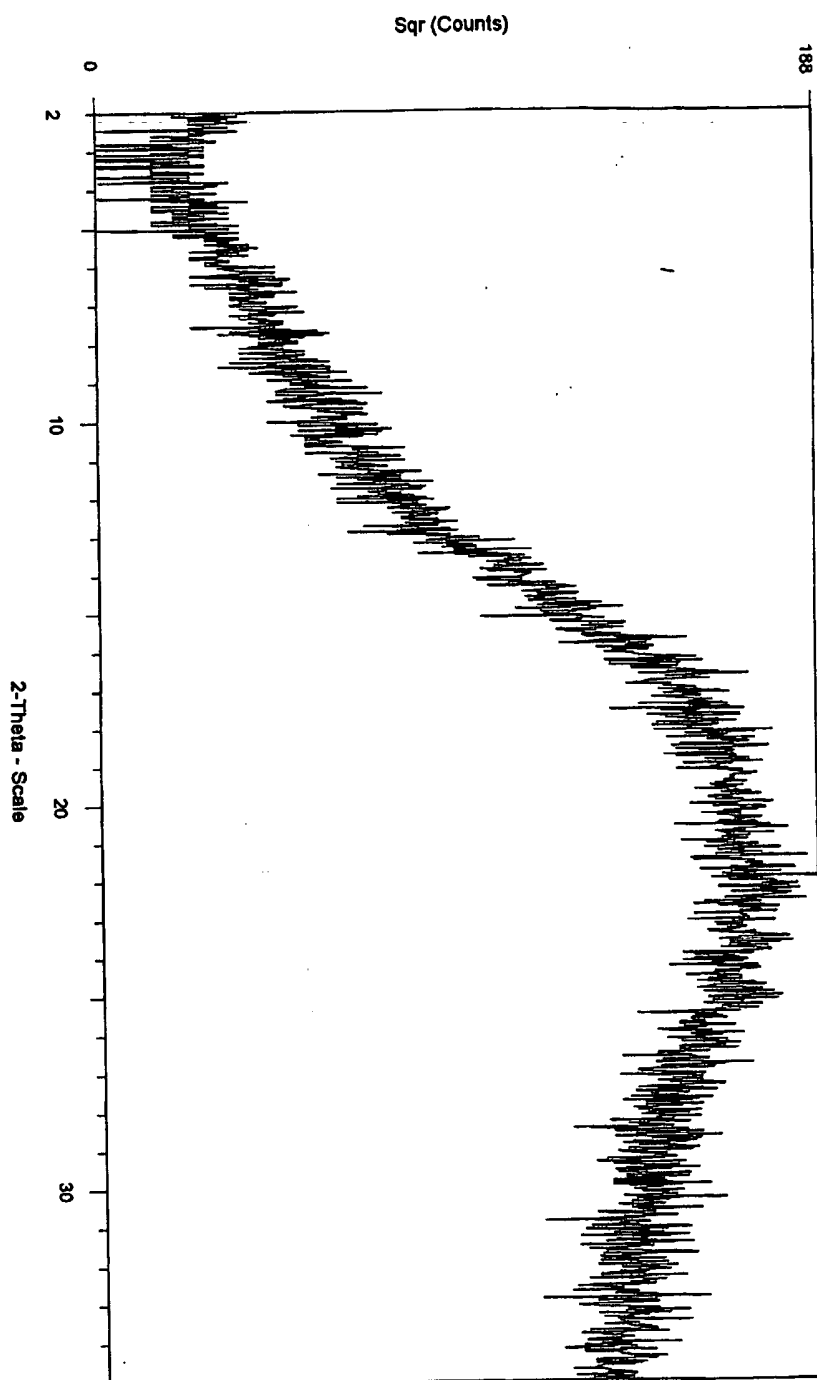


Figure 7 X-Ray Powder Diffractogram of the Citrate Hydrate 2



# INTERNATIONAL SEARCH REPORT

PCT/GB 02/05677

**A. CLASSIFICATION OF SUBJECT MATTER**  
IPC 7 C07D417/12 A61K31/4439 A61P3/10

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)  
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BEILSTEIN Data, WPI Data, EPO-Internal, CHEM ABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 306 228 A (BEECHAM GROUP PLC) 8 March 1989 (1989-03-08) cited in the application the whole document ---	1-32
Y	WO 94 05659 A (SMITHKLINE BEECHAM PLC) 17 March 1994 (1994-03-17) cited in the application the whole document ---	1-32
Y	WO 01 44240 A (RICHTER GEDEON VEGYÉSZETI GYÁR RT.) 21 June 2001 (2001-06-21) the whole document, particularly claim 7 --- -/--	1-32

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*G\* document member of the same patent family

Date of the actual completion of the international search

26 March 2003

Date of mailing of the international search report

04/04/2003

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Allard, M

## INTERNATIONAL SEARCH REPORT

PCT/GB 02/05677

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BERGE S M ET AL: "Pharmaceutical salts" JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 66, no. 1, 1977, pages 1-19, XP000562636 the whole document, particularly page 2, table I -----	1-32

# INTERNATIONAL SEARCH REPORT

PCT/GB 02/05677

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:  
  
Although claim 32 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:  
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

PCT/GB 02/05677

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Information on patent family members

PCT/GB 02/05677

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